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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,096	CAROZZI ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638 .	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19 and 22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,19 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Request for information

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 February 2008 has been entered.

2. Claims 1-11, 19 and 22-26 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Claims 1-11, 19 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:2, 4 and 6, host cells, plants, plant cells and seeds comprising them, and method of using them to make SEQ ID NO:2, 4 or 6, does not reasonably provide enablement for nucleic acids encoding pesticidal protein with 90% identity to SEQ ID NO:2, 4 and 6, or nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 90% identity to SEQ ID NO:2, 4 or 6 and a pesticidal protein encoded by a nucleic acid with 90% identity to SEQ ID NO:1, 3 or 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection is modified from the rejection set forth in the Office action mailed 14

November 2007. Applicant's arguments filed 13 February 2008 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding a pesticidal protein with 90% identity to SEQ ID NO:2, 4 or 6, nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5, or a complement of those nucleic acids, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 90% identity to SEQ ID NO:2, 4 or 6 and a pesticidal protein encoded by a nucleic acid with 90% identity to SEQ ID NO:1, 3 or 5.

The instant specification, however, only discusses sequencing of DNAs from non-publicly available bacterial strain ATX13026 (examples 1-4), identification of a nucleic acid, SEQ ID NO:1, that encodes a protein, SEQ ID NO:2, with 28% identity to the delta endotoxin cry8Aa, and an alternate start site variants, SEQ ID NO:4, which encode SEQ ID NOs:4 and 6, respectively (examples 5-6); assay of the protein for pesticidal activity against a number of pests, including the Coleopterans *D. virgifera virgifera* and *D. undecimpunctata*, the Hemipteran *T. ni*, and the Lepidopteran *L. lineolaris* (examples 7-12), and prophetic guidance for expression in plants (examples 13-15).

The instant specification fails to provide guidance for how to make the full scope of nucleic acids encoding pesticidal protein with 90% identity to SEQ ID NO:2, 4 or 6 or the full scope of nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5.

Nucleic acids encoding proteins with 90% identity to the 682 amino acid long SEQ ID NO:2 would encode proteins with 68 amino acid substitutions relative to SEQ ID NO:2. Similarly, nucleic acids encoding proteins with 90% identity to 671 amino acid long SEQ ID NO:4 would encode proteins with 67 amino acid substitutions, and nucleic acids encoding

proteins with 90% identity to 661 amino acid long SEQ ID NO:6 would encode proteins with 66 amino acid substitutions.

Nucleic acids with 90% identity to a 2049 nucleotide long nucleic acid like that of SEQ ID NO:1 would have 204 nucleotide substitutions, and thus encompass those that encode proteins with 204 amino acid substitutions relative to SEQ ID NO:2; these proteins would have 70% identity to SEQ ID NO:2. Similarly, nucleic acids with 90% identity to a 2016 nucleotide long nucleic acid like that of SEQ ID NO:3 would have 201 nucleotide substitutions, thus encompassing those that encode proteins with 201 amino acid substitutions, and nucleic acids with 90% identity to a 1986 nucleotide long nucleic acid like that of SEQ ID NO:5 would have 198 nucleotide substitutions, thus encompassing those that encode proteins with 198 amino acid substitutions.

Thus, the claims are drawn to nucleic acid that encode proteins with up to 204 amino acid substitutions relative to SEQ ID NO:2.

The instant specification fails to provide sufficient guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional protein.

The guidance in the specification with respect to making amino acids substitutions in AXMI-009 is as follows:

The specification, in the paragraph starting on pg 13, line 3, says:

> Amino acid substitutions may be made in nonconserved regions that retain function. In general, such substitutions would not be made for conserved amino acid residues, or for amino acid residues residing within a conserved motif, where such residues are essential for protein activity. Examples of residues that are conserved

and that may be essential for protein activity include, for example, residues that are identical between all proteins contained in the alignment of Figures 1A, B, and C. Examples of residues that are conserved but that may allow conservative amino acid substitutions and still retain activity include, for example, residues that have only conservative substitutions between all proteins contained in the alignment of Figures 1A, B, and C. However, one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues.

Conservative substitutions are defined on pg 12, lines 15-21. A search of the originally filed Fig. 1, shows that there are 2 positions that are identical among all the proteins in the Figure, and 8 positions that have only conservative substitutions among all proteins.

The specification on pg 12, lines 9-13 suggests that substitutions be made at amino acids that are not essential for biological activity, but does not teach any such amino acids.

The specification teaches the 5 highly conserved regions among endotoxins in AXMI-009 (specification pg 4, lines 6-12); the regions encompass a total of 130 amino acids.

Thus, from the guidance in the specification, it would appear that the majority of the amino acids in SEQ ID NO:2, 4 and 6 could be substituted.

The specification, on pg 17, lines 20-26, indicates that "variant" proteins, which include those with 70% and 90% identity to SEQ ID NO:2 "continue to possess the desired biological activity of the native protein that is, retaining pesticidal activity." This suggest that the that the protein should be pesticidal only to the pests to which SEQ ID NO:2 has activity, that is, *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris*.

However, although point mutations and substitutions of a few amino acids have been made in Cry proteins, no one has substituted up to 204 amino acids of a Cry protein, as encompassed the claimed nucleic acids.

Making amino acid substitutions in *cry* proteins is unpredictable. Each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol.

65:4369-4374, see pg 4369, column 1, paragraph 1), and even conservative substitutions in nonconserved regions can have unexpected effects on protein function (Figs 2 and 3). Even a single amino acid substitution in a *cry* protein may alter its insecticidal specificity, and toxicity must be determined empirically (Tounsi et al, 2003, J. Appl. Microbiol. 95:23-28; see pg 27, column 2, paragraph 2).

Aaronson et al (2001, FEMS Microbiol. Lett. 195:1-8) teach that there are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (paragraph spanning the columns on pg 7). de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). De Maagd et al (2001) concludes that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Thus, extensive teachings are required for making nucleic acids encoding *Cry* proteins with up to 204 amino acid substitutions relative to SEQ ID NO:2, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in *Cry* proteins by providing no working examples of proteins with up to 204 amino acid substitutions relative to AXMI-009.

The specification also suggests making the claimed nucleic acids by random mutagenesis (pg 13, lines 14-19. However, Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes,

increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins that have up to 204 random amino acid substitutions to find those that have pesticidal activity would require undue experimentation.

Thus, given the unpredictability making in amino acid substitutions in *cry* proteins, proteins with up to 204 amino acid substitutions relative to SEQ ID NO:2 would likely have a very different insect toxicity than AXMI-009, if such toxins could even be made. The specification does not teach the insect toxicity of such proteins. Therefore, one would not know how to use nucleic acids encoding proteins with up to 204 amino acid substitutions relative to SEQ ID NO:2.

As the specification does not describe the transformation of any plant with a pesticidal protein with 90% identity to SEQ ID NO:2, 4 or 6, nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with insect resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges they do not have to provide support for making a protein with up to 204 amino acid substitutions with no experimentation, only for making it with no undue experimentation (response pg7).

This is not found persuasive. The specification must teach how to make with up to 204 amino acid substitutions and produce a protein with *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris* toxicity without undue experimentation. Given the insufficient guidance in the specification, the unpredictability of making amino acid substitutions in Cry proteins and the lack of knowledge in the specification or the art of which amino acids are required for *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris* toxicity, it would require undue experimentation to make a protein with up to 204 amino acid substitutions.

Applicant urges *Wands* does not require a working example of every pesticidal protein that could be used to practice the present invention (response pg 8).

This is not found persuasive. A working example of every pesticidal protein that could be used to practice the present invention is not being required; a teaching of how to make the full scope of claimed nucleic acids that encode proteins with SEQ ID NO:2 biological activity, *i.e., D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris* toxicity, is required, however.

Applicant urges that sufficient guidance for making and using the recited sequences is present on pg 9-13, the sequences are limited by percent identity and function, Cry proteins are well-known, citing Crickmore, and the necessary techniques are routine (response pg 7-8).

This is not found persuasive. Limiting the percent identity of the claimed nucleic acid and requiring a function do not teach which amino acid substitutions may be made in the proteins. The guidance on pg 9-13 merely discusses fragment size, percent identity, and calculation of percent identity. However, guidance for determining percent identity does not teach the necessary and sufficient structural features of the claimed nucleic acids, and does not

teach which amino acids could be substituted with which other amino acids. The guidance on pg 11 and examples 7-12 fails to sufficiently teach which amino acid substitutions to make in SEQ ID NO:2, 4 or 6, given the unpredictability in making amino acid substitutions in cry proteins.

Further, according to the naming system defined by Crickmore, SEQ ID NO:2's 28% identity or less to other Cry proteins places it in a different primary rank than other Cry lineages (pg 808, left column, paragraph 2-4; Fig. 1), emphasizing the differences between SEQ ID NO:2 and other known Cry proteins. Making 204 amino acid substitutions in SEQ ID NO:2 and successfully making a functional cry protein is not taught by Crickmore or the cited portions of the specification.

Applicant urges that one would only need to make the claimed variants and assay them for activity using routine methods; thus the amount of experimentation is not undue, as it is possible to generate large numbers of sequences and test them (response pg 8).

This is not found persuasive because given the number of amino acid substitutions involved and the lack of teaching of the amino acids responsible for SEQ ID NO:2 biological activity, *i.e., D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris* toxicity, making and testing variants within the full scope of the claims would require undue experimentation.

Applicant urges that that *Genentech* states that the specification must supply the novel aspects of the invention, and in *Genentech* no starting materials were disclosed, while here there is a working example, guidance and reasonable detail; the absence of these are is undue experimentation (response pg 9).

This is not found persuasive. The instant rejection is a scope of enablement rejection; the invention is enabled for nucleic acid encoding SEQ ID NO:2 and SEQ ID NO:2 biological

activity, *i.e., D. virgifera virgifera, D. undecimpunctata, T. ni*, and *L. lineolaris* toxicity. The specification, however, does not provide adequate guidance for making up to 204 amino acid substitutions in SEQ ID NO:2. The art indicates that even though much is known about Cry protein structure, not enough is known about the structure/function relationship to predict a protein's toxicity.

Making the claimed variants and assaying them for activity would require undue experimentation because the specification does not provide sufficient guidance as to which up to 204 amino acid substitutions can be made in SEQ ID NO:2. Thus, one would need to randomly make nucleic acids encoding proteins with up to 204 amino acid substitutions and test them. Because this would require trail and error experimentation and because of the likelihood of protein inactivation (see Guo et al, pg 9209, right column, paragraph 2) and the unpredictability of amino acid interactions in cry proteins (Aaronson et al, paragraph spanning the columns on pg 7; de Maagd et al, 1999, pg 4369, column 1, paragraph 1; de Maagd et al, 2001, pg 194, right column, paragraph 3), this experimentation would be undue.

Applicant urges the specification provides a starting material and description regarding amino acid substitutions, in the form of conserved residues and domains and Fig 1 (response pg 9-10).

This is not found persuasive. Fig. 1 has only 2 positions that are identical among all the proteins in the Figure, and 8 positions that have only conservative substitutions, and the domains cover only 130 amino acids. Together, these amino acids total 20% of SEQ ID NO:2's length. The art indicates that more guidance is needed.

Comparison to the sequences in Fig 1 would not provide information of the structures

required for that function, as cry1Aa, cry1Ac, cry1Ca and cry1Ia are only toxic to Lepidopterans; cry3Aa, cry3Ba, cry3Bb, cry7Aa, and cry8Aa are only toxic towards Coleopterans; and cry4Aa, cry10Aa, cry16Aa, cry19Ba, cry24Aa and cry40Aa1 are toxic only to mosquitoes, which are Dipterans, and are not plant pests. A comparison of these with SEQ ID NO:2 provides no indication of the protein structures responsible for SEQ ID NO:2 biological activity.

The findings and teachings of Aaronson et al, Angsuthanasombat, de Maagd et al, Tounsi et al and de Maagd et al, 2001, as well as the references cited by Applicant in the response filed 16 October 2006 (Jenkins, Rajamohan, Lee, Schartz and Masson) show that interactions between amino acids in Cry proteins is much more complex than can be predicted from guidance suggesting only making conservative substitutions. De Maagd et al (2001) specifically teaches that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Applicant urges that in *Amgen* the Court acknowledges that disclosure of a few EPO genes justifies a claim encompassing those genes and similar analogs; here, disclosure of SEQ ID NO:2, 4, 6 justifies claims to those and analogs with 90% identity (response pg 10).

This is not found persuasive. The toxicity of the variant proteins encoded by the claimed nucleic acids is not known, nor can it be predicted. *Amgen* emphasized that the uncertainty as to what utility will be possessed by the analogs was part of the reason for needing more teaching. Only a very small proportion of proteins with 70% or 90% identity will have SEQ ID NO:2 biological activity, *i.e., D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris* toxicity, or even be toxic to plant pests. The specification does not teach how to make analogs within the full scope of the claims, and thus, does not justifies claims to analogs with 90%

identity to nucleic acids encoding SEQ ID NO:2, 4 or 6.

Applicant urges Guo's results only suggest that a large number of substitutions were not produced, not that they could not be; the instant specification provides guidance for which amino acids are not likely to tolerate random substitution (response pg 11).

This is not found persuasive. Guo's random mutagenesis method allowed substitutions wherever they could occur. Given that the probability that a single random amino acid substitution inactivates an enzyme is 34%, making up to 204 amino acid substitutions in SEQ ID NO:2 is unlikely to be successful. Further, the specification only indicates that about 140 amino acids of SEQ ID NO:2's 682 amino acid length are not likely to tolerate random substitution; however, the teachings of Guo et al, Aaronson et al, Angsuthanasombat, de Maagd et al, Tounsi et al and de Maagd et al, 2001 suggest otherwise.

Applicant urges detailed information about Cry secondary and tertiary protein structure was known, citing Li and Morse; they provide guidance for determining regions that would tolerate modification (response pg 11).

This is not found persuasive because general knowledge of Cry secondary and tertiary protein structure does not provide information on which amino acids are critical for toxicity toward the Coleopterans *Diabrotica virgifera virgifera* and *D. undecimpunctata*, the Lepidopteran *Trichoplusia ni*, and the Heteropteran *Lygus lineolaris*, which is the function taught in the specification (examples 10-12). Proteins with up to up to 204 amino acid substitutions relative to SEQ ID NO:2 would likely have a very different insect toxicity than AXMI-009, if such toxins could even be made.

It is noted that the protein taught by Li et al is a cry3Aa protein, which the instant

specification teaches has only 25% identity to SEQ ID NO:2 (Table 1), and that taught by Morse et al is a cry2Aa protein, which presumably has less than 5% identity to SEQ ID NO:2. This is relevant because de Maagd et al, 1999, teach that that the crystal structure of Cry1C only allows for limited prediction of the structure of Cry1Aa (pg 4373, right column, paragraph 4), which by Crickmore's nomenclature system would have between 45% and 78% identity to one another. Thus, the teachings of Li and Morse would have provide only limited guidance to one making 204 amino acid substitutions in SEQ ID NO:2.

Applicant urges that one could choose possible modifications based on the regions conserved among protein family members, then test for pesticidal activity (response pg 11-12).

This is not found persuasive because there are no family members for AXMI-009 (SEQ ID NO:2). The instant Table 1 shows that truncated AXMI-009 has 23-28% identity to a wide range of Cry toxins. According to the naming system defined by Crickmore, SEQ ID NO:2's less than 29% identity to other Cry proteins places it in a different primary rank to all these Cry lineages (pg 808, left column, paragraph 2-4; Fig. 1), emphasizing the differences between SEQ ID NO:2 and other known Cry proteins. Further, comparison to any of the Cry toxins listed in column 1 of Table 1 would not let one know which amino acids are critical for toxicity toward *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris*, the function of AXMI-009, as each of the listed toxins has a toxicity profile different from that of SEQ ID NO:2. Further, the list includes mosquito toxins, cry4Aa, cry10Aa, cry16Aa, cry19Ba, cry24Aa and cry40Aa1, and a protein with no known toxicity, cry25Aa.

Applicant urges that the indication that claims to nucleic acids encoding Cry proteins with a few amino acid substitutions would be enabled acknowledges that one of skill in the art

would know how to make and test variants; the same skills could be used to make and test variants with up to 204 amino acid substitutions (response pg 12).

This is not found persuasive. App;licant's claims are not limited to nucleic acids encoding Cry proteins with a few amino acid substitutions. Given the number of amino acid substitutions involved in the proteins encoded by the nucleic acids Applicant is claiming, and the lack of teaching of the amino acids responsible for SEQ ID NO:2 biological activity, *i.e., D. virgifera virgifera, D. undecimpunctata, T. ni*, and *L. lineolaris* toxicity, making and testing variants within the full scope of the claims would require undue experimentation.

5. Claims 1-11, 19 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection is modified from the rejection set forth in the Office action mailed 14 November 2007, in light of the new Written Description Guidelines. Applicant's arguments filed 13 February 2008 have been fully considered but they are not persuasive.

The claims all require nucleic acids encoding a pesticidal protein with 90% identity to SEQ ID NO:2, 4 or 6 and nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5, wherein the nucleic acid encodes a pesticidal protein. As nucleic acids encoding proteins with 90% identity to SEQ ID NO:2, 4 or 6 would encode proteins with up to 68 amino acid substitutions and nucleic acids with 90% identity to SEQ ID NO:1 encompass those that encode proteins with 204

amino acid substitutions relative to SEQ ID NO:2, the claims are drawn to a broad genus of nucleic acids.

The specification describes the 5 highly conserved regions among most Cry endotoxins; in the 682 amino acid long SEQ ID NO:2, the regions encompass a total of 130 amino acids (specification pg 4, lines 6-12).

The specification, on pg 17, lines 20-26, indicates that "variant" proteins, which include those with 70% and 90% identity to SEQ ID NO:2 "continue to possess the desired biological activity of the native protein that is, retaining pesticidal activity." This suggest that the that the protein should be pesticidal only to the pests to which SEQ ID NO:2 has activity, that is, *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris*.

The specification describes no relevant characteristics or motifs responsible for activity towards *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris*.

Aaronson et al (2001, FEMS Microbiol. Lett. 195:1-8) teach that there are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (paragraph spanning the columns on pg 7). de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). de Maagd et al (2001) concludes that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2). Further, each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1)

The specification does not describe the structure required for the recited function, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5 from other nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5 or pesticidal proteins with 90% identity to SEQ ID NO:2, 4 or 6 from other proteins with 90% identity to SEQ ID NO:2, 4 or 6.

The only species reduced to practice in the specification is SEQ ID NO:1, 3 or 5, which encodes SEQ ID NO:2, 4 or 6. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1, 3 or 5 alone is insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described nucleic acids encoding a pesticidal protein with 90% identity to SEQ ID NO:2, 4 or 6 and nucleic acids with 90% identity to SEQ ID NO:1, 3 or 5, wherein the nucleic acid encodes a pesticidal protein, within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges the claims recite percent identity, for which the methods for determining are routine; many Cry proteins are known in the art, as are their structures and functions associated with particular structures, regions and motif, citing pg 2, 9-13 and the Fig 1 legend (response pg 13-14).

This is not found persuasive because the structures associated with particular the

disclosed function, toxicity toward the Coleopterans *Diabrotica virgifera virgifera* and *D. undecimpunctata*, the Lepidopteran *Trichoplusia ni*, and the Heteropteran *Lygus lineolaris*, are not known in the art or described in the specification. Comparison to the sequences in Fig 1 would not provide information of the structures required for that function, as cry1Aa, cry1Ac, cry1Ca and cry1Ia are only toxic to Lepidopterans; cry3Aa, cry3Ba, cry3Bb, cry7Aa, and cry8Aa are only toxic towards Coleopterans; and cry4Aa, cry10Aa, cry16Aa, cry19Ba, cry24Aa and cry40Aa1 are toxic only to mosquitoes, which are Dipterans, and are not plant pests. A comparison of these with SEQ ID NO:2 provides no indication of the protein structures responsible for SEQ ID NO:2 biological activity.

Applicant urges that it was known that Cry proteins have three domains, a helix bundle, a three-sheet domain and a beta sandwich motif, citing Li, providing very specific and define structural parameters to the claimed sequences (response pg 14).

This is not found persuasive. These general characteristics are true of every Cry protein, including those with toxicity to lepidopterans, coleopterans, nematodes and mosquitoes and those native proteins that do not appear to have any toxicity at all (*e.g.*, cry25Aa). These basic structures are merely characteristics of Cry proteins. They are not specifically associated with the disclosed function, *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris* toxicity. de Maagd et al (2001) teaches that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2). Additionally, it is noted that the claims are not limited to nucleic acids encoding Cry proteins.

Applicant urges relevant motifs were known, including the domains taught by Li, and conserved regions taught in the specification (response pg 14).

This is not found persuasive because Li et al does not describe the structural features responsible for the claimed function. de Maagd et al, 1999, teach that that the crystal structure of Cry1C only allows for limited prediction of the exact structure of Cry1Aa (pg 4373, right column, paragraph 4); thus, Li's teaching is insufficient for describing the structure/function relationship of the claimed nucleic acids. More than the Crystal structure and conserved regions are required for Cry protein function. These regions do not describe the protein structures responsible for SEQ ID NO:2 biological activity, *D. virgifera virgifera*, *D. undecimpunctata*, *T. ni*, and *L. lineolaris* toxicity.

Applicant urges individual support for each species is not required; they have provided exemplary nucleotide and amino acid sequences and variants and fragments thereof, and numerous Cry proteins were known in the art, allowing one to envision that claimed invention (response pg 14-15).

This is not found persuasive because those of skill in the art say that the relationship between structure and function is not well-known in Cry proteins. Aaronson et al, de Maagd et al, 1999, and de Maagd et al, 2001, make it clear that the correlation between that function and a structure is not sufficiently known in cry proteins as a whole, and the specification does not describe the motifs and amino acids required for SEQ ID NO:2 biological activity. The specification does not make up for this deficit.

Applicant urges the recitation of a predictable structure is sufficient to satisfy the written description requirement (response pg 15).

This is not found persuasive because the correlation between structure and function is also required, but not provided by the instant specification. The relationship between structure

and the specific pesticidal function was not described in the specification.

Applicant urges the claim recite functional characteristics that distinguish the claimed sequences, as well as fragments (response pg 15-16).

This is not found persuasive. The recitation of the function does not describe the structures responsible for it.

Request for Information under 37 CFR § 1.105

6. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

This request is being made for the following reasons:

Applicant is claiming a nucleic acid with 90% identity to a nucleic acid isolated from *Bacillus thuringiensis* strain ATX13026, but the instant specification is silent about the source of *B. thuringiensis* strain ATX13026. The requested information is required to make a meaningful and complete search of the prior art.

In response to this requirement, please provide answers to each of the following interrogatories eliciting factual information:

(i) What is the source of *B. thuringiensis* strain ATX13026? Please supply all of the designations/denominations used for this strain.

(ii) At or before the time of filing of the instant application or any provisional application to which benefit is claimed, had said *B. thuringiensis* strain ATX13026 been disclosed or made publicly available? If so, under what designation/denomination and under what

conditions were said strain been disclosed or made publicly available and from when to when?

If Applicant views any or all of the above requested information as a Trade Secret, then Applicant should follow the guidance of MPEP § 724.02 when submitting the requested information.

In responding to those requirements that require copies of documents, where the document is a bound text or a single article over 50 pages, the requirement may be met by providing copies of those pages that provide the particular subject matter indicated in the requirement, or where such subject matter is not indicated, the subject matter found in applicant's disclosure. Please indicate where the relevant information can be found.

The fee and certification requirements of 37 CFR § 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR § 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR § 1.105 are subject to the fee and certification requirements of 37 CFR § 1.97.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR § 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Anne Kubelik, Ph.D.
May 7, 2008

/Anne R. Kubelik/
Primary Examiner, Art Unit 1638